REMARKS

Allowable Subject Matter

In the May 28, 2004 Office Action, Examiner Davis found claim 26 to be free of prior art and to meet all requirements of patentability. Applicant requests that method claims 29, 30 and 32, all of which depend from claim 26 and thus include all the limitations of claim 26, be examined and found allowable.

Rejections of Claims and Traversal Thereof

In the May 28, 2004 Office Action,

claims 1-3, 20, 22 and 27-28 were rejected under 35 U.S.C. §112, first paragraph.

This rejection is hereby traversed, and reconsideration of the patentability of amended claims herein is requested, in light of the ensuing remarks.

Rejection under 35 U.S.C. §112, first paragraph

A. According to the Office: "claims 1-3, 20, 22 and 27 are not enabled for a polypeptide that induces cell death *in vitro* consisting of SEQ ID NO: 1 or 2 or a variant thereof." Applicant has amended the rejected claims, thereby obviating this rejection and requests the withdrawal of the rejection under 35 U.S.C. §112.

B. According to the Office: "Claims 20, 28 are not enabled for a variant of SEQ ID NO: 2 or 8." Applicant has amended claims 20 and 28 as set forth below:

> 20. An isolated variant of SEQ ID NO. 8, wherein the variant is characterized by (1) at least 95% identity to SEQ. ID NO. 8 (2) a conserved carboxy end region having an amino acid sequence of amino acid residues 353 to 405 of SEQ ID NO. 8, (3) conservative changes in any amino acid substitutions and (4) induces cell death *in vitro*.
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> 28. An isolated variant of the polypeptide of claim 26, wherein the variant is characterized by (1) at least 95 % identity to SEQ. ID NO. 8, (2) conservative changes in amino acid substitutions and (3) induces cell death *in vitro*.

The Office contends that variants of SEQ ID NO: 8 as recited in claims 20 and 28 do not meet the enablement requirements of 35 U.S.C. §112, first paragraph. Applicant vigorously disagrees.

The first paragraph of 35 U.S.C. §112 requires, *inter alia,* that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without "undue experimentation."In *re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). A number of factors are relevant to whether undue experimentation would be required to practice a claimed invention, including "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

Reviewing the Wand factors will show that one skilled in the art can practice the presently claimed invention without undue experimentation. Initially, it should be noted that the claims, as now written, are limited to variants of SEQ ID NO. 8 that also must include at least the following limitations:

(1) at least 95% identity to SEQ. ID NO. 8;
(2) conservative changes in any amino acid substitutions; and
(3) induces cell death *in vitro*.

Clearly, the recited parameters encompass a limited amount number of variants. The variants will not include SEQ ID NO: 2 because SEQ ID NO: 2 does not have 95% homology with SEQ ID NO: 8. SEQ ID NO: 2 comprises 53 amino acid residues and SEQ ID NO: 8 has over 400 amino acid residues. The variants of SEQ ID NO: 8, as recited in claim 28, include conservative changes in the amino acid substitutions. As stated in the present specification, a "substitution," is defined as the replacement of one or more amino acids by different amino acids. As such, substitution is limited to replacement and does not include deletion or additional amino acid residues, as proposed by the Office. Further, in the specification, conservative substitutions are described as certain amino acid sequence substitutions in a polypeptide sequence that can be made and still obtain a polypeptide with similar functional properties. Exemplary substitutions that maintain such similar functional properties are well known to those of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine and additional conservation substitutions are set forth in Table 1 in the specification. Clearly, by following the guidance set forth in the application (see Table 1), amino acid substitutions in the variants, include amino acid residues that do not alter the biological functionality.

The biological activity, that being, the ability to induce cell death can be very easily determined by one skilled in the art, and the specification provides guidance as set forth in Example 2. One skilled in the art will easily have the knowledge and skills to include a nucleotide sequence that will express a variant of SEQ ID NO: 8, suspected of having the capability of inducing cell death, in a tissue culture cell transfection vector to be expressed in a cell. Expression of a variant in a transfected cell will provide an immediate indication of it functionality by inducing cell death. Applicant has not included an example for each and every possible variant but it is well settled in the law that a working example is not required for every single embodiment of the invention, especially if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice (See *In re Borkowski*, 164 USPQ 642 (CCPA 1970) and *United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Thus, the breath of the claims is not broader than that described in the specification and the quantity of experimentation to practice the full scope of the claims does not require undue experimentation.

Further, there is adequate guidance and working examples. The specification provides guidance regarding how to make and use a functional variant. Clearly, the level of skill in this field is very high and one skilled in the art is very aware of conservation substitutions of amino acid residues. As such, information known by one skilled in the art will provide ample assistance in practicing the claimed invention, and as such, known prior art contributes significantly to the enabling scope of the disclosure. Moreover, as stated by the Office at page 35 of the December 11, 2003 Office Action, Sambrook, et al. provides methods for elucidating structure-function relationships by analyzing the properties of normal and mutant proteins.

According to the Office, "protein chemistry is highly unpredictable and that a change of even a single amino acid could dramatically affect the biological activity of a protein, as taught by Bowie, et al, Burgess. et al. and Lazar, et al." However, the Office has overlooked the fact that when conservative substitutions were included in the mutants discussed in the three cited references, the conservative substitution did not eliminate activity but in fact merely reduced activity. For example, in Lazar, et al., when aspartic acid was replaced with serine or glutamic acid (a conservative substitution according to applicant's specification), the mutant had reduced activity. When leucine 48 was mutated to alanine (not considered to be a conservative substitution) there was a complete loss of activity. However, when leucine 48 was substituted with a conservative replacement, the activity was merely reduced. Thus, the conservative replacement provided for functional activity, albeit at reduced activity. It should be noted that there is no rule that all activity must be the same for all substitutions to meet the requirements of 35 U.S.C. §112, first paragraph, and one skilled in the art can easily determine the activity and choose the most effective variant.

Regarding the substitutions described in the Burgess, et al. reference, the results show a change in lysine 132 to a glutamic acid residue caused a drastic reduction in activity of HBGF-1. However, this is not surprising because glutamic acid is not considered to be a conservative substitution of lysine. Notably, if the substitution had been an arginine, recognized as a conservative substitution according to disclosure in Table 1 of applicant's application, the outcome of the functional activity may have been very different.

Bowie, et al., provides further support for the importance of conservative substitutions as discussed in column 2, page 247:

> "For example, in studying the effects of approximately 1500 single amino acid substitutions at 142 positions in *lac* repressor, Miller and co-workers found that about one-half of all substitutions were phenotypically silent (11). At some positions, many different, nonconservative substitutions were allowed. Such residue positions play little or no role in structure and functions. At other positions, no substitutions or only conservative substitutions were allowed."

Bowie, et al. further discusses, in the next paragraph, that when a residue is changed from Asp to Asn there was a 10^4 -fold reduction in activity. Likewise when a Asn residue was changed to a Asp residue there was also a loss of activity. This is not surprising considering the Asp is not considered to be a conservative substitute for Asn, nor is Asn considered to be a conservative substitute for Asp. Clearly, the references cited by the Office provides further credence to applicant's approach that all amino acid substitutions must be conservative.

Applicant submits that the claimed invention, including the variants of SEQ ID NO: 8 meet both the enablement requirements and the written description requirements under 35 U.S.C. §112, first paragraph. Notably, the Office agrees because no rejection for lack of written description was imposed. A quick review of Example 14, in the written description guidelines provided by the USPTO shows that the amended claims for the variants of SEQ ID NO: 8, meet the written description requirements.

The analysis section of this example, states;

> "A review of the full content of the specification indicates that a protein having SEQ ID NO: 3 or variants having 95% identity to SEQ ID NO: 3 and having catalytic activity are essential to the operation of the claimed invention. The procedure for making variants of SEQ ID NO: 3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO: 3 which have 95%

> identity to SEQ ID NO: 3 and retain its activity are conventional in the art."

The guidelines further state that one skilled in the art would conclude that applicant was in possession of the necessary common attributes possessed by the member of the genus.

Importantly, the correlation and interconnection between the written description requirements and enablement requirements under 35 U.S.C. §112, first paragraph, have recently been discussed by the Court in *Moba B.V. v. Diamond Automation, Inc.*, 66 USPQ2d 1429 (Fed. Cir. 2003), specifically by Judge Rader in his concurring opinion. Judge Radar was discussing the *Lilly*[1] decision and written description requirements and stated that:

> "[T]he only way to distinguish the *Lilly* rule from enablement is to construe *Lilly* as requiring more disclosure than necessary to enable one of skill in the art to make and use the invention, a "super-enablement" standard." [2]
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> "After all, to enable is to show possession, and to show possession is to enable."

Clearly, in light of Judge Radar's remark, if the claims meet the written description requirement in biotechnology then the claims certainly and inherently meet the enablement requirements. Therefore, the instant application provides sufficient and enabling information for a person of ordinary skill in the art to practice applicant's invention as recited in claims 20 and 28. Applicant respectfully requests the withdrawal of this rejection under §112, first paragraph.

Rejoining of Method Claims

Applicant is requesting that all method and use claims that are currently withdrawn be rejoined and examined according to the guidelines set forth in Section 821.04 of the MPEP. This section in the MPEP states that when elected product claims are found to recite patentable subject matter then all method claims for making and/or using the products may be rejoined and examined in this one application provided the method of making and using claims recite the product found to be patentable during examination of the elected invention. Thus understood, applicant requests that because all product claims as currently amended are patentable, the method and use claims are to be rejoined and taken up for examination. Applicant has amended the method claims during the prosecution of this application

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[1] *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997)

2 Mueller, Janice M., "The Evolving Application of the Written Description Requirement to Biotechnological Inventions" 13 *Berkeley Tech. L.J.* 615, 617 (Spring 1998) ("The *Lilly* decision establishes uniquely rigorous rules for the description of biotechnological subject matter that significantly contort written description doctrine away from its historic origins and policy grounding. The *Lilly* court elevate[s] written description to an effective 'super enablement' standard ....").

and as such are ready for examination. Claims 13, 21, 23-24, 29, 30 and 32 are fully enabled by the specification and Example 2.

Fees Payable

In the event any fee or charge is properly payable in connection with the entry of this Amendment the United States Patent and Trademark Office is hereby authorized to charge the amount to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

Conclusion

Applicant has satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Davis reconsider the patentability of claims 1, 2, 13, 20-21, 23-24 and 26-32 in light of the distinguishing remarks herein, and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Davis is requested to contact the undersigned attorney at (919) 419-9350 to resolve same.

Respectfully submitted,

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